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ACUTE RESPIRATORY DISTRESS SYNDROME IN A PATIENT WITH *LEGIONELLA PNEUMOPHILA*. A CASE REPORT

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Abstract: *Patients suffering from pneumonia caused by Legionella pneumophila may experience severe progression, which can lead to acute respiratory distress syndrome and necessitate intensive care unit admission. The diagnosis of Legionnaires' disease relies on clinical presentation and laboratory tests. The urinary antigen test is a primary diagnostic tool for Legionnaires' disease, providing rapid results with high specificity for L. pneumophila serogroup 1. Employing multiple diagnostic methods enhances diagnostic accuracy, particularly in cases where L. pneumophila serogroup 1 is not the causative agent. Among pro-inflammatory cytokines, IL-6 plays a crucial role in the immune response to Legionella pneumophila infection and is associated with the severity of the inflammatory response in Legionnaires' disease. We report on a patient who was admitted to the intensive care unit due to hypoxemic respiratory failure resulting from Legionnaires' disease. Although the urinary antigen test came back negative, Legionella was strongly suspected based on clinical, paraclinical, and epidemiological evidence, leading to the initiation of targeted antibiotic treatment. The diagnosis was ultimately confirmed through serology. The severity of the inflammatory response was evaluated by measuring serum biomarkers, among them IL-6 levels. This case report outlines the clinical and laboratory parameters that guide intensive care practices.*

Key words: *Legionella pneumophila, respiratory failure, ARDS, IL-6*

1. Introduction

Legionella pneumophila, the causative agent of Legionnaires' disease, is a pathogen replicating within free-living amoebae and human alveolar macrophages and is responsible for sporadic and

community-acquired pneumonia (CAP) [1, 2]. *Legionella* pneumonia can lead to

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the development of acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS) [3].

As it transitions between intracellular and extracellular environments, the bacterium undergoes cellular differentiation, which is linked to virulence and metabolism [4].

Legionella is found mainly in water samples with temperatures ranging from 30 to 40 degrees Celsius, and infections in humans occur by inhalation of aerosols, from air conditioning systems, cooling towers, spas, fountains, ice machines, plant sprayers, dental appliances, and showerheads [3], [5].

Severe Legionella pneumonia is characterized by a hyper-inflammatory phase and immunoparalysis, with elevated levels of certain cytokines associated with disease severity [6].

In 2016, the Third International Consensus Definitions for Sepsis defined sepsis as life-threatening organ dysfunction that develops due to an impaired host response to infection [7]. Organ dysfunction can be identified as an acute change in the total Sequential Organ Failure Assessment (SOFA) score ≥ 2 points [8].

Some studies consider interleukin-6, a cytokine generated by immune cells, as a potential triage test for sepsis, enabling the timely initiation of empirical antibiotic therapy for ICU patients while awaiting culture results [8].

The mortality rate for patients with Legionella pneumonia in the ICU is high, varying between 9.1% and 41.7% [9].

The diagnosis of Legionnaires' disease is based on a combination of clinical presentation, epidemiologic criteria, and laboratory tests. The urinary antigen test (UAT) is a primary diagnostic tool for Legionnaires' disease. It detects the presence of Legionella pneumophila antigens in urine samples [2], [10].

There are many serogroups of Legionella pneumophila (L. pneumophila), but most Urinary Antigen Tests only detect L. pneumophila serogroup 1. Consequently, patients with pneumonia caused by other serogroups usually receive negative results on Legionella urinary antigen detection tests [5, 11].

Other diagnostic methods include polymerase chain reaction (PCR), which has the disadvantage of limited commercial availability; cultures, which are slow and technically challenging; direct fluorescent antibody tests, for which reagents are difficult to obtain; and serology, with the caveat that antibodies may be shared across species and serogroups [12].

Regarding antibiotic therapy, observational studies on patients with severe pneumonia recommend Legionella-targeted antibiotics to be included in the empiric regimen [9].

2. Case presentation

A 55-year-old female patient with a normal weight (BMI 21.9 kg/m²) and a known history of arterial hypertension (treated with Telmisartan 40 mg/day) presented to the Emergency Department of Clinical Emergency Military Hospital "Regina Maria" Braşov with high-grade fever (40°C), dry cough, marked asthenia, myalgia, and arthralgia. The symptoms

debuted three days before admission. The history revealed that the patient recently travelled to the United Arab Emirates.

In the Emergency department, the patient exhibited tachypnea, a blood oxygen saturation of 90% on room air, and bilateral basal crackles upon auscultation.

The patient presented with leukocytosis, neutrophilia, and a high C-reactive protein level on admission. Arterial blood gas analysis showed hypoxemia, with an oxygen pressure in arterial blood of 75 mmHg, a partial pressure of carbon dioxide of 32 mmHg, and a lactate of 1.3 mmol/L.

The patient tested negative for SARS-CoV-2, Influenza type A and B, Respiratory Syncytial Virus (RSV), and had negative Human Immunodeficiency Virus (HIV) serology.

The chest X-ray showed a right-sided paracardiac pulmonary consolidation (Figure 1).

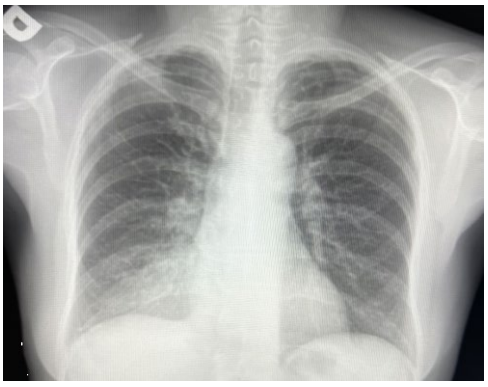

Fig. 1. *Chest X-ray on admission showing a right-sided pulmonary consolidation*

Hemodynamically, the patient was stable and had a sinus rhythm. The CURB-65 severity score was 1 point.

The patient was started on empiric intravenous antibiotics: Ceftriaxone 2g/day and Gentamicin 240 mg/day.

After two days, the patient developed severe ARDS with a PaO2/FiO2 ratio of 70 and was transferred to the Intensive Care Unit.

The CT thorax examination revealed bilateral, multilobar ground-glass opacification (Figure 2).

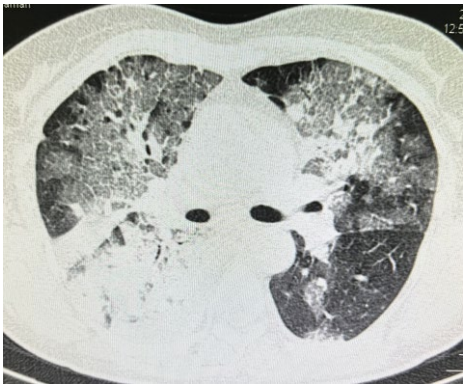

Fig.2. *Computer tomography of the lungs showing bilateral opacification*

Hemodynamic stability was maintained during the patient's admission to the intensive care unit.

Respiratory failure was initially managed with high-flow oxygen delivered through a nasal cannula and non-invasive mechanical ventilation.

Figure 3 illustrates the evolution of the PaO2/FiO2 ratio and A-a gradient, with remission of ARDS occurring on day 7 of the ICU stay.

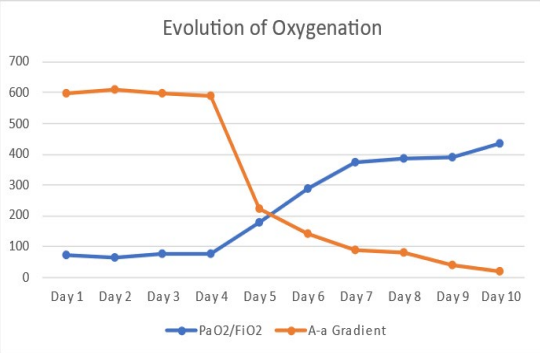

Fig. 3. *Dinamics of PaO2/FiO2 and A-a gradient*

Legionella was suspected based on clinical, paraclinical, and epidemiological aspects, including prolonged exposure to air conditioning. Levofloxacin 1000 mg was initiated daily, and the patient also received corticosteroid therapy.

The urinary antigen test yielded a negative result, and blood cultures displayed no growth. No other pertinent pathological specimens were available for culture. The patient required twelve days of intensive care, with favorable clinical and paraclinical evolution while on Levofloxacin.

The diagnosis was ultimately confirmed retrospectively four weeks after admission via serology, revealing serum IgM antibodies at 6.1 index units (with the test indicating positivity at values above 0.8 based on the Enzyme Immunoassay method).

IL-6 levels were dynamically measured to assess the evolution of the inflammatory response. As illustrated in Figure 4, the IL-6 and PaO2/FiO2 ratio dynamics are divergent.

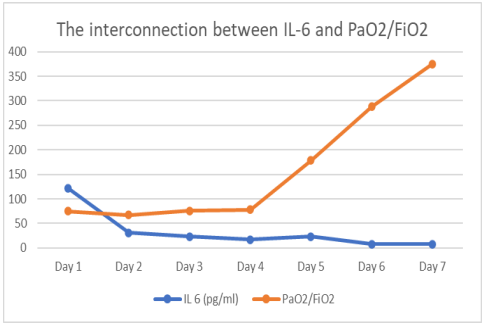

Fig.4. *Severity of disease evolution*

Regarding the behavior of inflammatory markers, it's worth mentioning that once Levofloxacin therapy began, C-reactive protein exhibited a gradual decline. In contrast, IL-6 responded quickly, with a significant drop in serum concentration (Figure 5).

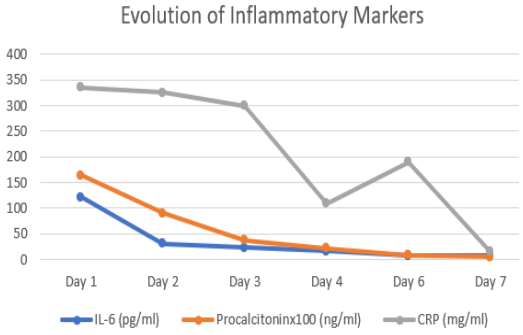

Fig.5. *Evolution of inflammatory serum biomarkers*

Concerning the dynamics of white blood cells, a peak was observed on day 3, followed by a decline with the start of Levofloxacin therapy (Figure 6).

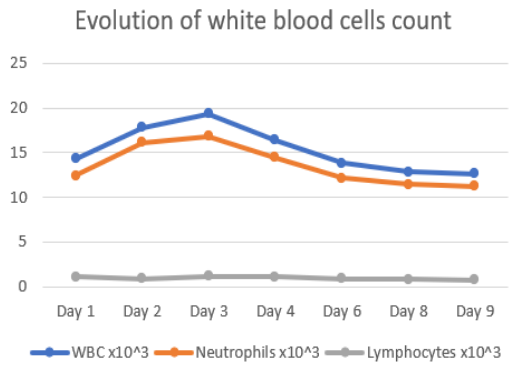

Fig.6. *Evolution of white blood cells count*

3. Discussion

Legionellae are aerobic, gram-negative bacilli measuring 0.3 to 0.9 micrometers wide and 2 to 20 micrometers long [13]. L. pneumophila is a significant cause of disease in humans, while L. longbeachae and a few other species can occasionally cause pneumonia [12]. The antigenic specificity of L. pneumophila arises from its complex antigenic structures [14].

Different species exhibit cross-reactive antigenicity, and researchers have identified 16 serogroups of L. pneumophila. Notably, serogroup 1 was linked to the 1976 Legionnaires' disease outbreak and remains the most frequently isolated serogroup from humans [5], [12], [15].

The pathogenicity of Legionella is complex, affecting homeostasis and leading to significant metabolic perturbations that compromise host cellular function [16].

Legionella is known to alter glucose utilization, leading to changes in cellular energy production. It affects protein synthesis and degradation, which in turn has implications for immune defence, and it can modify membrane composition and function. Thus, there are complex host-pathogen interactions [16].

Diagnostic tools for Legionnaire's disease have advanced through the utilization of the UAT and techniques that identify all Legionella serogroups [17].

There were several diagnostic challenges in our case. First, clinical and imaging findings were nonspecific. The patient had no immune risk factors for Legionellosis, which added to the diagnostic complexity.

The urinary antigen test was negative. The antigen urinary test is widely used due to its rapid results and high specificity for L. pneumophila serogroup 1, which is responsible for over 85% of Legionnaires' disease cases worldwide [4].

Legionella does not grow on standard culture media; it requires buffered charcoal yeast extract (BCYE) agar and incubation for 3–5 days.

Finally, the diagnosis was ultimately confirmed retrospectively through serology by the presence of positive IgM Legionella Pneumophila antibodies.

Despite a challenging course, once the diagnosis was established, the patient gradually improved with supportive therapy and targeted antimicrobial treatment.

Polymerase chain reaction (PCR) testing on respiratory samples, such as sputum, tracheal aspirates, or broncho-alveolar lavages, is another important diagnostic method. PCR can detect the presence of Legionella DNA in these samples, allowing for a more sensitive diagnosis [10].

Isolation of Legionella from respiratory samples through culture on selective media is considered a definitive diagnostic method. Specifically, buffered charcoal yeast extract selective medium is used for Legionella bacteria [10].

Due to the high mortality associated with untreated Legionnaire's disease, it is recommended that Legionella respiratory culture be sent as part of the initial evaluation for suspected Legionella pneumonia in patients with severe pneumonia, as well as routine UAT for those with severe community-acquired pneumonia [9], [15], [18].

For our patient, sputum samples could not be obtained for molecular and bacteriologic diagnosis.

The difficulty of the case comes from the delayed detection of antibodies because most patients develop anti-*Legionella* antibodies around 3 weeks after the onset of the disease [3].

While not specific to Legionnaires' disease, clinical symptoms of pneumonia and radiological evidence of pulmonary infiltrates on chest X-rays are important components of the diagnostic process, added to the epidemiological context [10].

Multiple diagnostic methods increase the accuracy of diagnosis, especially in cases where L. pneumophila serogroup 1 is not the causative agent.

Early targeted antibiotic treatment is critical. A study published in 2020 on 116 patients with Legionella infections showed that the early administration of an antibiotic regimen containing at least one drug active against Legionella (macrolides or levofloxacin) significantly reduces the risk of ICU admission [2].

Another study showed that progression of non-severe Legionella pneumonia to the severe form is favored by low platelet count and delayed antibiotic treatment [19].

From the intensivist's perspective, the particularity of this severe ARDS case was that respiratory failure management was accomplished without the need for intubation and invasive mechanical ventilation.

Another particularity was that procalcitonin trends were not clinically informative, while IL-6 dynamics correlated with inflammatory and clinical disease progression.

Due to diagnostic uncertainty, this case required complex multidisciplinary collaboration between clinicians, laboratory specialists, and radiologists.

4. Conclusion

This case underscores the diagnostic limitations in detecting Legionella infections, particularly when relying solely on urinary antigen tests. It highlights the necessity for a high index of suspicion in instances of severe pneumonia with poor initial progression. Multidisciplinary teamwork was crucial in both diagnosis and management, facilitating a favorable outcome despite significant respiratory compromise.

References

1. Chauhan D., Shames S.R.. Pathogenicity and Virulence of Legionella: Intracellular replication and host response. *Virulence*, 2021; **12**(1): 1122-1144.
2. Falcone M. et al. Predictors of intensive care unit admission in patients with Legionella pneumonia: role of the time to appropriate antibiotic therapy. *Infection*, 2021; **49**(2): 321-325.
3. Yue R. et al. Early Detection of Legionella pneumophila and Aspergillus by mNGS in a Critically Ill Patient With Legionella Pneumonia After Extracorporeal Membrane Oxygenation Treatment: Case Report and Literature Review. *Frontiers in Medicine*, 2021; **Vol. 8 .**
4. Oliva G., Sahr T., Buchrieser C. The Life Cycle of L. pneumophila: Cellular Differentiation Is Linked to Virulence and Metabolism. *Front Cell Infect Microbiol*, 2018: **8**: p.3.
5. Talapko J. et al. Legionella pneumophila-Virulence Factors and the Possibility of Infection in Dental Practice. *Microorganisms*, 2022; **10**(2).
6. Allam C. et al, Hyper-inflammatory profile and immunoparalysis in patients with severe Legionnaires' disease. *Front Cell Infect Microbiol*, 2023; **13**: p. 1252515.
7. Kilinc Toker A., Kose S., Turken M. Comparison of SOFA Score, SIRS, qSOFA, and qSOFA + L Criteria in the Diagnosis and Prognosis of Sepsis. *Eurasian J Med.*, 2021; **53**(1): 40-47.
8. Molano Franco D. et al. Plasma interleukin-6 concentration for the diagnosis of sepsis in critically ill adults. *Cochrane Database Syst Rev,* 2019; **4**(4): Cd011811.
9. Andrea L. et al. Legionella Pneumonia in the ICU: A Tertiary Care Center Experience Over 10 Years. *Crit Care Explor*, 2021; **3**(8): e0508.
10. Rello J. et al. Community-acquired Legionella Pneumonia in the intensive care unit: Impact on survival of combined antibiotic therapy. *Med Intensiva*, 2013; **37**(5): 320-326.
11. Kim P., Deshpande A., Rothberg M.B. Urinary Antigen Testing for Respiratory Infections: Current Perspectives on Utility and Limitations. *Infect Drug Resist*, 2022; **15**: 2219-2228.
12. Ha R. et al. The Adequacy of Current Legionnaires' Disease Diagnostic Practices in Capturing the Epidemiology of Clinically Relevant Legionella: A Scoping Review. *Pathogens*, 2024; **13**(10).
13. Marrie T.J. 322 - Legionella Infections, in Goldman's Cecil Medicine (Twenty Fourth Edition), L. Goldman and A.I. Schafer, Editors. 2012, W.B. Saunders: Philadelphia, p. 1903-1906.
14. Otten S. et al. Serospecific antigens of Legionella pneumophila. *J Bacteriol*, 1986; **167**(3): 893-904.
15. Viasus D. et al. Legionnaires' Disease: Update on Diagnosis and Treatment. *Infect Dis Ther*, 2022; **11**(3): 973-986.
16. Wang Z. et al. Insights into the role of legionella effectors on host metabolic perturbations. *Front Cell Infect Microbiol*, 2024; **14**: 1458276.

17. Rello J. et al. Severe Legionnaires' disease. *Ann Intensive Care*, 2024; **14**(1): 51.
18. Pedro-Botet M.L. and Yu V.L. Treatment strategies for Legionella infection. *Expert Opin Pharmacother*, 2009. **10**(7): 1109-21.
19. Huh J.Y. et al. Incidence and risk factors associated with progression to severe pneumonia among adults with non-severe Legionella pneumonia. *Acute Crit Care*, 2022; **37**(4): 543-549.